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Cardiotoxicity after anticancer treatment

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Document Version

Publisher's PDF, also known as Version of record

Publication date:

2005

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Perik, P. J. (2005). *Cardiotoxicity after anticancer treatment: clinical investigations and molecular mechanisms*. s.n.

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EXPERIMENTAL ANIMAL MODEL FOR ANTHRACYCLINE-INDUCED HEART FAILURE

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EUROPEAN JOURNAL OF HEART FAILURE 2004;6:375-376

The paper by Simunek et al. in this issue of the Journal describes a rabbit model for heart failure (HF), in which HF is caused by anthracycline-induced cardiomyocyte damage.¹ The discovery of the presence of both apoptosis,² and proliferation³ in cardiac myocytes in the human heart, contested the general assumption that the heart is a terminally differentiated organ. With this in mind, animal models of cardiomyocyte injury, such as the rabbit model described by Simunek et al. in this issue, may be of great interest to evaluate alternative, previously unexplored pathophysiologic mechanisms of HF and to test new cardioprotective treatment modalities.

The authors describe that systolic and diastolic cardiac function were impaired in daunorubicin treated rabbits, in contrast to saline-treated controls. Assessment of cardiac function was performed by cardiac catheterization, phonocardiography, echocardiography, biochemistry, and histological examinations of the rabbit hearts after sacrifice.¹ It was possible to adequately quantify severity of HF, and higher cumulative doses of daunorubicin resulted in increased impairment of cardiac function. The authors rightly conclude that this model is of value for studying drug cardiotoxicity and for the evaluation of cardioprotective agents. However, with regard to the clinical value of the model, some observations must be taken into account. First, in the rabbits, HF developed early during daunorubicin treatment, whereas in patients this is generally a long-term effect. Second, the rabbits received 3 mg/kg body weight daunorubicin intravenously, weekly for 10 weeks, resulting in a cumulative dose of 90 mg/m², which is rather low for humans, who normally receive up to 450-550 mg/m² cumulative life-time dose. The fact that all daunorubicin-treated animals developed HF during treatment, and with the rather low dose, indicates that rabbits are more susceptible to anthracycline cardiotoxicity than humans. Furthermore, the weekly treatment schedules in the rabbits may be completely not comparable to patient regimes (usually 3-weekly administrations in 4-6 cycles). Finally, nephrotoxicity, which occurred in daunorubicin-treated rabbits, is not a relevant side effect in anthracycline-treated patients.

Anthracyclines are among the most effective anticancer compounds and are therefore widely used in current antitumor therapy. In both curative and palliative settings, use of anthracyclines is increasing, for example in the adjuvant breast cancer treatment. The most important limitation in the use of anthracyclines in clinical practice is cardiotoxicity. Due to the current awareness of dose-dependent cardiotoxicity, the administration of high cumulative amounts of anthracyclines in patients is usually avoided. Furthermore, cardiac function is often monitored during anthracycline treatment. Nevertheless, even low cumulative amounts of anthracyclines can cause substantial cardiac damage.⁴

Use of cardioprotectants may enable the safer administration of high cumulative amounts of anthracyclines.⁵ The consequence of the use of these agents may be, however, that the cardioprotective effects are accompanied by a reduction of antitumor efficacy of chemotherapeutic agents. For the development of new cardioprotectants animal models, such as the model described in this issue, can thus

be used for a careful preclinical selection of effective cardioprotective agents and to support the optimal design for clinical trials. Large randomized clinical trials with long-term follow-up to prove cardioprotective effects that do not interfere with antitumor efficacy of the chemotherapeutic agents, can then be reserved for proven effective compounds.⁶ Cardiomyocyte apoptosis plays an important role in anthracycline-induced cardiotoxicity,⁷ therefore, new cardioprotectants may be developed that aim to inhibit apoptotic mechanisms, such as free radical formation-induced lipid peroxidases and/ or calcium influx in the cell through ceramide pathway-activated B-type calcium channels.^{8,9}

In conclusion, animal models, such as the rabbit model described by Simunek et al., may be of importance for studying the role of apoptotic pathways in the heart and for preclinical evaluation of new cardioprotective compounds.

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